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A convenient synthesis of 2-substituted indoles by the reaction of 2-(chloromethyl)phenyl isocyanides with organolithiums

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ABSTRACT

The reaction of 2-(chloromethyl)phenyl isocyanides, readily available by dehydration of the respective *N*-[2-(chloromethyl)phenyl]formamides, with organolithiums produced 2-substituted indoles in satisfactory yields through addition of organolithiums to the isocyano carbon followed by intramolecular substitution reaction of the resulting imidoyl anion intermediates.

1. Introduction

Indoles are undoubtedly very important heterocycles in organic synthesis. Therefore, development of new and efficient methods for the general preparation of indoles has been the subject of intense research.[1] In this paper we wish to describe that a new and convenient method for the preparation of 2-substituted indoles, which is based on reactions of 2-(chloromethyl)phenyl isocyanides with organolithiums, has been developed. The utility of *ortho*-functionalized phenyl isocyanides in heterocycle synthesis is well established.[2–5] In particular, Fukuyama and Tokuyama have elegantly demonstrated the utility of 2-isocyanosrtyrene derivatives in the synthesis of indole derivatives including natural products.[2] A synthesis of 2,3-disubstituted quinolines through cyclization of 2-alkynylisocyanobenzenes has been reported by Ito and Suginome.[3] Ichikawa has reported syntheses of 3-fluoroquinoline derivatives based on reactions utilizing β-difluoro-2-isocyanostyrenes.[4] However, there have been few reports on utilization of 2-(chloromethyl)phenyl isocyanides in organic synthesis so far, though 2-(chloromethyl)phenyl isocyanide has been used in the synthesis of 1- and 2-platinum(II)-substituted indole derivatives by Michelin and colleagues.[6] To the best of our knowledge, the present report is the first example of the practical use of these isocyanide in organic synthesis.

2. Results and discussion

Our preparation of 2-substituted indoles **3** was conducted as illustrated in Scheme 1. The starting materials of the present synthesis, *N*-(2-chlorophenyl)formamides **1**, were easily prepared by formylation of 2-aminobenzyl alcohols with ethyl or butyl formate followed by chlorination with thionyl chloride. These formamides **1** were converted into 2-(chloromethyl)phenyl isocyanides **2** on treatment with phosphorous oxychloride in the presence of triethylamine in THF.[7] Because these isocyanides **2** were unstable under purification conditions (distillation and chromatography on silica gel), they were used in the next step without any purification after the usual workup as soon as possible. Thus, crude isocyanides **2** were allowed to react with three molar amounts of organolithiums in THF at −78 °C. After stirring for 2 h, the usual workup gave, after purification of preparative TLC on silica gel, the desired products **3**. The results are summarized in Scheme 1, which indicates that overall yields of **3** from **1** are generally moderate-to-fair. When 5-chloro-2-(chloromethyl)phenyl isocyanide (**2b**) was used, somewhat higher yields of the corresponding desired indoles **3** were obtained, compared to those using other 2-(chloromethyl)phenyl isocyanides **2a** and **2c**. These results may be attributed to higher reactivity of the isocyano carbon toward nucleophiles due to the chloro substituent on the benzene ring.

The formation of 2-substituted indoles **3** is induced by attack of an organolithium at the isocyano carbon of 2-(chloromethyl)phenyl isocyanides **2** to generate the imidoyl anion intermediate **4**, as depicted in Scheme 2. This intermediate undergoes intramolecular

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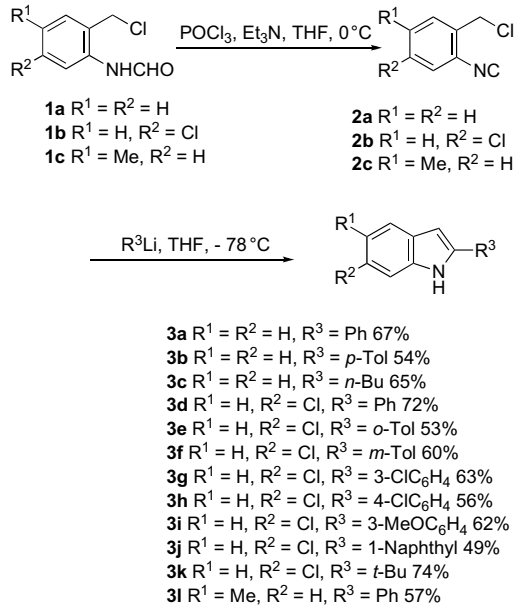
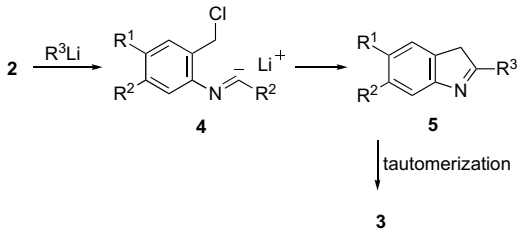


Scheme 1.



Scheme 2.

S_N2 reaction to give the indolenine intermediate **5**, which, probably, tautomerized during workup and/or purification procedures to afford **3**. The possibility of lithiation of **5** to an indolyllithium intermediate with excess organolithium is excluded, because addition of iodomethane to the reaction mixture did not give the corresponding *N*-methyl derivatives. The use of three molar amounts of organolithiums is essential for the satisfactory production of the desired products. With less than three molar amounts of organolithiums the reaction sequence did not proceed in a satisfactory manner and gave mixtures of only rather decreased yields of the desired products and the starting materials. One of the probable reasons for the modest yields of the products may be ascribed to somewhat lower purity of 2-(chloromethyl)phenyl isocyanides used without purification; no other products, whose structures could be determined, were isolated. Although the reason for the necessity of excess organolithiums in the present reaction is not clear, the uses of excess nucleophiles have often be reported in the heterocycle synthesis initiated by the attack of nucleophiles on the isocyano carbon.[4b,5f] When the reaction sequence was carried out in diethyl ether or 1,2-dimethoxyethane, an intractable mixture of products including ones probably arising from deprotonation of the benzyl proton of **2** was obtained in each case. No trace of **3** was isolated from this mixture. Grignard reagents, such as phenylmagnesium bromide and ethylmagnesium bromide did not work well in the present indole formation to give a complex reaction mixture in each case.

In conclusion, the results described above have shown that the synthesis of 2-substituted indoles is conveniently accomplished from readily available 2-(chloromethyl)phenyl isocyanides. We believe that this procedure may be value in organic synthesis because of its simplicity.

3. Experimental

3.1. General

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low- and high-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3.2. Starting materials

N-[2-(Chloromethyl)phenyl]formamide (**1a**) was prepared by the reported method[1] from *N*-[2-(hydroxymethyl)phenyl]-formamide,[6] which was prepared by treating 2-aminobenzylalcohol with refluxing ethyl formate. 2-Amino-4-chlorobenzyl alcohol[8] was prepared by the LAH reduction of ethyl 2-amino-4-chlorobenzoate.[9] All other chemicals used in this study were commercially available.

*3.2.1. 1-Chloromethyl-2-isocyanobenzene (**2a**)[6,10]*

This compound was prepared from *N*-[2-(chloromethyl)-phenyl]formamide[6] by a modified procedure[7a] of Ugi's method.[7b] Thus, to a stirred solution of *N*-[2-(chloromethyl)phenyl]formamide (0.30 g, 1.8 mmol) in THF (6 mL) containing Et_3N (1.3 g, 12 mmol) at 0 °C was added $POCl_3$. After 10 min the mixture was treated with saturated aqueous $NaHCO_3$ (15 mL) and extracted with Et_2O twice (10 mL each). The combined extracts were washed with saturated aqueous $NaHCO_3$ and then brine, and dried over anhydrous K_2CO_3. After evaporation of the solvent the residue (a brown liquid) was used in the next step without any purification.

3.2.2. N-[5-Chloro-2-(hydroxymethyl)phenyl]formamide

This compound was prepared by treating 2-amino-4-chlorobenzyl alcohol with refluxing ethyl formate in 66% yield; a white solid; mp 124–126 °C (hexane–Et_2O); IR (KBr) 3300, 1682 cm^{-1}; ^{1}H NMR δ 1.68 (br s, 1H), 4.72 and 4.73 (2s, combined 2H), 7.06–8.68 (m, 5H). Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.70; H, 4.39; N, 7.32.

*3.2.3. N-[5-Chloro-2-(chloromethyl)phenyl]formamide (**1b**)*

This compound was prepared by treating *N*-[5-chloro-2-(hydroxymethyl)phenyl]formamide with $SOCl_2$ according to the reported procedure[1] in 55% yield; mp 95–97 °C (hexane–Et_2O); IR (KBr) 3279, 1665 cm^{-1}; ^{1}H NMR δ 4.57 and 4.59 (2s, combined 2H), 7.14–8.61 (m, 5H). Anal. Calcd for $C_8H_7C_2NO$: C, 47.09; H, 3.46; N, 6.86. Found: C, 46.93; H, 3.51; N, 6.61.

*3.2.4. 1-Chloro-4-chloromethyl-3-isocyanobenzene (**2b**)*

This compound was prepared from *N*-[5-chloro-2-(chloromethyl)phenyl]formamide by a similar procedure as described for the preparation of **2a**, and used in the next step without any purification after the usual workup; a brown liquid; IR (neat) 2121 cm^{-1}; ^{1}H NMR δ 4.67 (s, 2H), 7.42 (dd, J=8.2, 2.3 Hz, 1H), 7.44 (d, J=2.3 Hz, 1H), 7.47 (d, J=8.2 Hz, 1H); MS m/z 185 (M^+, 100). HRMS Calcd for $C_8H_5Cl_2N$: M, 184.9799. Found: m/z 184.9776.